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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,771	02/20/2002	David R. Cox	UCSF-127CIP2	4176

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EXAMINER

CALAMITA, HEATHER

ART UNIT PAPER NUMBER

1637

DATE MAILED: 12/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,771	COX ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 3, 2005, has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 27-47 are currently pending and under examination. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "at least about 5 nucleotides in length". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that values above and below 16 nucleotides are permitted. Further, the extent of variance permitted by "about" is unclear in this context. Since nucleotides are whole numbers, "about 5" cannot mean from 4.4 to 6.6 because nucleotides cannot be split in half. Therefore, it is also unclear if "about 5" simply includes 4 or if it also includes 1-3 as well. In Amgen, Inc. v. Chugai

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Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

4. Claims 27-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for markers with mismatches of at least 5 nucleotides where the second mismatch is four nucleotides or less, does not reasonably provide enablement for markers of four or less mismatched nucleotides where the second mismatch is four nucleotides or less. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detecting mismatches by the use of in vivo mismatch repair where a second marker sequence with a mismatch is also present in a multiplex assay. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The invention is a method of mismatch detection in which a mismatch between two DNA strands of interest is detected by corepair of the mismatch of interest and a mismatch of at least about 5 nucleotides in a detectable marker. The claims are broadly drawn to mismatches of any length (except for claim 39 where the mismatch is a single nucleotide polymorphism) and where the detectable marker mismatch can also be of any length.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of mismatch repair systems. Since the only mismatch repair system used requires at least 5 nucleotides in the marker sequence and less than 5 nucleotides in the corepair mismatch segment, performance of the method as current claimed, where these nucleotide requirements are absent, would require identification of a new mismatch repair system in a new organism. Screening for such a new mismatch repair system would require years of inventive effort, with many intervening steps, without any reasonable expectation that there could be effective reduction to practice in finding such a new mismatch repair system and with no guarantee of success in any of the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art of Parker et al (Proc. Natl. Acad. Sci. (1992) 89:1730-1734) teaches that mismatches of 1-4 nucleotides are repaired while mismatches of 5 nucleotides are not repaired by the E. coli dam directed mismatch system (abstract). Parker further notes that mismatches of 7, 9 and 11 bases are also not repaired by this system (page 1733, last paragraph to page 1734, first paragraph). The claimed method requires that the mutation in the detectable marker be unreparable without a second mismatch or the method will yield unpredictable results. The results will be unpredictable because the following scenarios may result. In the classic method, a 5 bp mismatch in the detectable marker and a 1 bp

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mismatch in the DNAs of interest will yield corepair of both and activation of the marker, while with a 5 bp mismatch in the detectable marker and no mismatch in the DNAs of interest, there will be no activation of the marker. If 3 or 4 bp mismatches are used in the detectable marker and a 1 bp mismatch occurs in the DNAs of interest, there should be corepair to yield activation of the marker. However, in the control situation here, where a 3 or 4 bp mismatch is present in the marker but no mismatch in the DNAs of interest, the *E. coli* dam directed mismatch system may repair the mismatch and yield activation of the marker. Thus, no information will be conveyed about the state of mismatch of the DNAs of interest because, while a null result will mean no mismatch, a positive result may or may not mean a mismatch is present in the DNAs of interest. The method, using 3 or 4 bp mismatches, will therefore yield an unpredictable result.

Working Examples

There are no working examples of mismatches of less than 5 nucleotides in the specification.

Guidance in the Specification.

The specification provides working examples and guidance for situations in which the mismatch in the marker gene is 5 nucleotides or greater, but provides not teaching or guidance of mismatches less than 5 nucleotides. In fact, the specification clearly states “*E. coli* detects single point misniatches as well as one-, two-, and three-nucleotide loops, but it does not detect loops of 5 nucleotides or more. (see page 7, lines 10-11 of the specification).”

Level of Skill in the Art

The level of skill in the art is deemed to be high.

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Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching against the use of less than 5 nucleotide marker mismatches by the art is opposed to patentability (see Parker). It is therefore concluded that the scope of the invention is limited to at least 5 bp mismatches in the detectable marker since a large amount of experimentation is required due to the breadth of the claim to include less than 5 bp mismatches, and since there is an absence of guidance in the specification, an absence of working examples, as well as negative teachings in the prior art of Parker and the high level of unpredictability balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Summary

5. No claims were allowed.

Correspondence

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.


Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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hgc


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PRIMARY EXAMINER
12/1/05